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|            |                    |                  | Application Number     | 10/579,160        |
| INFO       | RMATION [          | DISCLOSURE       | Filing Date            | March 1, 2007     |
| STAT       | <b>TEMENT BY</b>   | APPLICANT        | First Named Inventor   | Mary Ellen Rybak  |
|            |                    |                  | Art Unit               | 1623              |
|            | (Use as many shee  | ts as necessary) | Examiner Name          | Lewis, Patrick T. |
| Sheet      | 1                  | of 11            | Attorney Docket Number | 13566.105023      |

|                        |     |  | U.S. PATENT [                  | OCUMENTS   |   |  |
|------------------------|-----|--|--------------------------------|--|---|--|
| Examiner<br>Initials * |     | Document Number                            | Publication Date<br>MM-DD-YYYY | Name of Patentee or Applicant of<br>Cited Document | Pages, Columns, Lines, Where Relevant<br>Passages or Relevant |  |
| IIIIIais               | NO. | Number - Kind Code <sup>2</sup> (if known) | WIIWI-DD-1111                  |  | Figures Appear  |  |
|                        |     | US-20020137663                             | 9/26/2002                      | Forman et al.                                      |   |  |
|                        |     | US- 20040019027                            | 1/29/2004                      | Forman et al.                                      |   |  |
|                        |     | US- 20060030571                            | 2/9/2006                       | Rinehart   |   |  |
|                        |     | US- 20060094687                            | 5/4/2006                       | Beijnen  |   |  |
|                        |     | US- 20070004691                            | 1/4/2007                       | Donald   |   |  |
|                        |     | US- 20070082856                            | 4/12/2007                      | Gianni   |   |  |
|                        |     | US- 20070128201                            | 6/7/2007                       | D'Incalci et al.                                   |   |  |
|                        |     | US-5,089,273                               | 2/18/1992                      | Rinehart et al.                                    |   |  |
|                        |     | US-5,149,804                               | 9/22/1992                      | Rinehart et al.                                    |   |  |
|                        |     | US-5,256,663                               | 10/26/1993                     | Rinehart et al.                                    |   |  |
|                        |     | US-5,478,932                               | 12/26/1995                     | Rinehart et al.                                    |   |  |
|                        |     | US- 5,552,544                              | 9/3/1996                       | Brana Fernandez et al.                             |   |  |
|                        |     | US-5,654,426                               | 8/5/1997                       | Rinehart et al.                                    |   |  |
|                        |     | US-5,721,362                               | 2/24/1998                      | Corey et al.                                       |   |  |
|                        |     | US-5,985,876                               | 11/16/1999                     | Rinehart et al.                                    |   |  |
|                        |     | US-6,124,293                               | 9/26/2000                      | Rinehart et al.                                    |   |  |
|                        |     | US- 6,153,590                              | 11/28/2000                     | Andersen et al.                                    |   |  |

|               | FOREIGN PATENT DOCUMENTS |  |                             |                                |  |       |  |  |
|---------------|--------------------------|--|-----------------------------|--------------------------------|--|-------|--|--|
| Examiner Cite | Cite                     | Cito Foreign Patent Document   |                             | Name of Patentee or            | Pages, Columns, Lines,<br>Where Relevant |       |  |  |
| Initials*     | No. <sup>1</sup>         | Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> ( <i>if known</i> ) | Publication Date MM-DD-YYYY | Applicant of Cited<br>Document | Passages or Relevant<br>Figures Appear   | $T^6$ |  |  |
|               |                          | WO 99/58125  | 11/18/1999                  | Rinehart et al.                |  |       |  |  |
|               |                          | WO 99/51238  | 10/14/1999                  | Rinehart et al.                |  |       |  |  |
|               |                          | WO 01/77115  | 10/18/2001                  | Flores et al.                  |  |       |  |  |
|               |                          | WO 02/64843  | 08/22/2002                  | Haygood et al.                 |  |       |  |  |
|               |                          | WO 05/49029  | 6/2/2005                    | Gianni et al.                  |  |       |  |  |
|               |                          | WO 05/49030  | 6/2/2005                    | Rowinsky et al.                |  |       |  |  |
|               |                          | WO 05/49031  | 6/2/2005                    | Rybak et al.                   |  |       |  |  |
|               |                          | WO 06/35244  | 4/6/2006                    | Allavena et al.                |  |       |  |  |
|               |                          | WO 06/46080  | 5/4/2006                    | Gilles et al.                  |  |       |  |  |

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|               | (Use as many she   | ets as | necessary) | Examiner Name          | Lewis, Patrick T. |
| Sheet 2 of 11 |                    |        |            | Attorney Docket Number | 13566.105023      |

|                        |                          | NON PATENT LITERATURE DOCUMENTS   |                |
|------------------------|--------------------------|---|----------------|
| Examiner<br>Initials * | Cite<br>No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T <sup>2</sup> |
|                        |                          | Akers, "Excipient -Drug Interactions in Parenteral Formulations," Journal of Pharmaceutical Sciences, 91(11), pp. 2283-2300, Nov. 2002  |                |
|                        |                          | Barrera, H. et al., "Interaction of ET-743 and standard cytotoxic agents against a panel of human tumor cell lines," Proceedings of the American Association for Cancer Research, Volume 40, page 591, Abstract No. 3896, March 1999                            |                |
|                        |                          | Biroccio et al., "Telomere Dysfunction Increases Cisplatin and Ecteinascidin-743 Sensitivity of Melanoma Cells," Molecular Pharmacology, 63:632-638 (2003)  |                |
|                        |                          | Blay et al., "Combination of Trabectedin and Doxorubicin for the Treatment of Patients with Soft Tissue Sarcoma: Safety and Efficacy Analysis," 43 <sup>rd</sup> annual ASCO meeting, June 1-5, 2007  |                |
|                        |                          | Bonfanti et al., "Effect ofEcteinascidin-743 on the Interaction Between DNA Binding Proteins and DNA." Anticancer Drug Des. 14, 179-86, 1999  |                |
|                        |                          | Bowman, A. et al., "Phase I clinical and pharmacokinetic (PK) study of ecteinascidin-743 (ET-743) given as a one hour infusion every 21 days," Annals Oncology, Abstract 452, 1998  |                |
|                        |                          | Brandon et al., "In-vitro Cytotoxicity of ET-743 (Trabectedin, Yondelis), a Marine Anti-cancer Drug, in the Hep G2 Cell Line: Influence of Cytochrome P450 and Phase II Inhibition, and Cytochrome P450 Induction, Anti-cancer Drugs, 16:935-943 (2005).        |                |
|                        |                          | Burstein et al., "Phase I study of Doxil and Vinorelbine in Metastatic Breast Cancer," Annals of Oncology, vol. 10, pages 1113-1116, 1999, XP8086751  |                |
|                        |                          | European Agency for the Evaluation of Medicinal Products, "Committee for Proprietary Medicinal Products Summary of Opinion for Yondelis", November 20, 2003   |                |
|                        |                          | Corey et al., "Enantioselective Total Synthesis of Ecteinascidin 743", J. Am. Chem. Soc., 118, 9202-9203, 1996  |                |
|                        |                          | Cvitkovic, E. et al., "Final results of a phase I study of ecteinascidin-743 (ET-743) 24 hour (h) continuous infusion (CI) in advanced solid tumors (AST) patients (pts)," 1999 ASCO Annual Meeting Proceedings, Abstract No. 690, May 15-18, 1999              |                |
|                        |                          | Cvitkovic, E. et al., "Ecteinascidin-743 (ET-743) 24 hour continuous intravenous infusion (CI) phase I study in solid tumors (ST) patients," Annals Oncology, Abstract 456, 1998  |                |

| Substitute | for form 1449A/PTC | )      |            |                        | Complete if Known |
|------------|--------------------|--------|------------|------------------------|-------------------|
|            |                    |        |            | Application Number     | 10/579,160        |
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|                        |                          | NON PATENT LITERATURE DOCUMENTS   |                |
|------------------------|--------------------------|---|----------------|
| Examiner<br>Initials * | Cite<br>No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.  Delaloge, S. et al., "Ecteinascidin-743: A Marine-Derived Compound in Advanced Pretreated Sarcoma Patients-Preliminary Evidence of Activity", J. of Clinical Oncology, vol. 19, no. 5, pp. 1248-1255, 2001 | T <sup>2</sup> |
|                        |                          | DeVita et al., "Combination Versus Single Agent Chemotherapy: A Review of the Basis for Selection of Drug Treatment of Cancer", Cancer, vol. 35, pp. 98-110, 1975   |                |
|                        |                          | D'Incalci et al., "The Combination of ET-743 and Cisplatin (DDP): From a Molecular Pharmacology Study to a Phase I Clinical Trial," from the AACR Annual Meeting of April 6-10, 2002, Abstract 404.   |                |
|                        |                          | D'Incalci et al., "Preclinical and Clinical Results with the Natural Marine Product ET-743," Expert Opin. Investig. Drugs, 12(11):1843-1853 (2003).   |                |
|                        |                          | D'Incalci et al., "In human tumor xenografts the resistance to ET-743 or to cisplatin can be overcome by giving the two drugs in combination," European Journal of Cancer, 38, Suppl. 7, 34 (November 2002)   |                |
|                        |                          | D'Incalci et al., "The combination of yondelis and cisplatin is synergistic against human tumor xenografts," European Journal of Cancer 39: 1920-1926 (2003).   |                |
|                        |                          | Donald et al., "Complete Protection By High-Dose Dexamethasone Against The Hepatotoxicity of the Novel Antitumor Drug Yondelis (ET-743) in The Rat," Cancer Research, Vol. 63, p. 5902-5908, September 2003   |                |
|                        |                          | Donald et al., "Dietary Agent Indole-3-Carbinol Protects Female Rats Against the Hepatotoxicity of the Antitumor Drug ET-743 (trabectidin) Without Compromising Efficacy in a Rat Mammary Carcinoma" International Journal Of Cancer,_Vo1. 111, No.6, p. 961-967, 2004  |                |
|                        |                          | Dorr and Van Hoff, "Doxorubicin," Cancer Chemotherapy Handbook, 1994, pp. 395-416   |                |
|                        |                          | "Doxil (doxorubicin Hcl Liposome Injection) Product Information", October 10, 2004, pages 1-16, XP002389462, < <webselength* 20041009180="" web="" web.archive.org="">&gt;</webselength*>   |                |
|                        |                          | Drugs Fut., "Ecteinascidin-743" vol. 22, no. 11, page 1279, 1997  |                |
|                        |                          | Eckhardt et al., "In vitro Studies of a Novel Marine Cytotoxic, Ecteinascidin (ET-743)," New Drugs and Pharmacology, Annals of Oncology, 7 (Suppl. 5), 131, Abstract 632P (1996).   |                |
|                        |                          | Endo et al., "Total Synthesis of Ecteinascidin 743", J. Am. Chem. Soc., 124, 6552-6554, 2002  |                |
|                        |                          | Erba et al., "Synergistic cytotoxic effect of ET-743 and cisplatin," Clinical Cancer Research, Vol. 6, Abstract 209 (November 2000).  |                |

| Substitute for form 1449A/PTO     |                        | Complete if Known |
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|                                   | Art Unit               | 1623              |
| (Use as many sheets as necessary) | Examiner Name          | Lewis, Patrick T. |
| Sheet 4 of 11                     | Attorney Docket Number | 13566.105023      |

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|                        |              | Erba et al., "Combination of yondelis (ET-743) and oxaliplatin in experimental ovarian cancer," from the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics of Nov. 17-21, 2003, Abstract C247  |                |
|                        |              | Erba et al., "ET-743 and Cisplatin (DDP) Show in Vitro and in Vivo Synergy Against Human Sarcoma and Ovarian Carcinoma Cell Lines," from the AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics of October 29 – November 2, 2001, Abstract 406.   |                |
|                        |              | Erlichman, C., "18: Pharmacology of Anticancer Drugs," The Basic Science of Oncology, 2nd edition, Tannock et al., editors, McGraw-Hill, New York, pages 317-337, 1992  |                |
|                        |              | FDA approved label for Pharmacia and Upjohn's Doxorubicin Hydrochloride for Injection (May 8, 2003).  |                |
|                        |              | Faircloth et al., "In Vivo Combinations of Chemotherapeutic Agents with Ecteinascidin 743 (ET743) Against Solid Tumors," from the Proceedings AACR-NCI-EORTC of November 2001, Abstract 387.  |                |
|                        |              | Faircloth et al., "Dexamethasone Potentiates the Activity of Ecteinascidin 743 in Preclinical Melanoma and Osteosarcoma Models," Abstract and Presentation 379 (2002).  |                |
|                        |              | Faulkner et al., "Symbiotic Bacteria in Sponges: Sources of Bioactive Substances," Drugs from the Sea, Fusetani, N. (ed.), Basel Karger, 2000, pp. 107-119  |                |
|                        |              | Fayette et al., "ET-743: a Novel Agent with Activity in Soft-Tissue Sarcomas," Current Opinion in Oncology, 18:347-353 (2006).  |                |
|                        |              | Fourouzesh, B. et al., "Phase I and pharmacokinetic study of the marine-derived DNA minor groove binder ET-743 on a weekly x3 every-4-week schedule in patients with advanced solid malignancies," Proceedings of the 2001 AACR-NCI-EOTRC International Conference, Abstract No. 209, October 29-November 2, 2001 |                |
|                        |              | Fourouzesh, B. et al., "Phase I and pharmacokinetic study of ET-743, a minor groove DNA binder, administrated weekly to patients with advanced cancer," Proc Am Soc Clin Oncol, vol 20, 2001 ASCO Annual Meeting Proceedings, Abstract No. 373, 2001  |                |
|                        |              | Forouzesh, B., et al., "Phase I and pharmacokinetic study of ET-743, a minor groove DNA binder, administered weekly to patients with advanced cancer," European Journal of Cancer, ECCO 11, volume 37, supplement 6, Abstract No. 106, October 21-25, 2001  |                |

| Substitute             | for form 1449A/PTO | )      |            |                        | Complete if Known |
|------------------------|--------------------|--------|------------|------------------------|-------------------|
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|                        |                          | NON PATENT LITERATURE DOCUMENTS  |                |
|------------------------|--------------------------|--|----------------|
| Examiner<br>Initials * | Cite<br>No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.  | T <sup>2</sup> |
|                        |                          | Friereich et al., "Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man," Cancer Chemotherapy Reports, 50:4, May 1966, pp.219-245   |                |
|                        |                          | Fukuyama et al., "Total Synthesis of Saframycin A," J. Am. Chem. Soc., 112, 3712-3713, 1990  |                |
|                        |                          | Fukuyama et al.,"Stereocontrolled Total Synthesis of Saframycin B," J. Am. Chem. Soc., 104, 4957-4958, 1982  |                |
|                        |                          | Garcia Gravalos, M.D., et al., "In vitro schedule-dependent cytotoxicity by ecteinascidin 743 (ET-743) against human tumor cells," 23rd European Society for Medical Oncology Congress, Abstract No. 652, November 6-10, 1998  |                |
|                        |                          | Ghielmini, M. et al., "Schedule-dependent myelotoxicity induced in vitro by the new marine derived minor groove interacting agent ecteinascidin 743," ECCO, vol. 9, Abstract No. 807, September 17, 1997   |                |
|                        |                          | Ghielmini, M. et al., "In vitro schedule-dependency of myelotoxicity and cytotoxicity of Ecteinascidin 743 (ET-743)," Annals of Oncology, vol. 9, pages 989-993, 1998  |                |
|                        |                          | Gianni et al. "Definition of the Least Toxic Sequence and Optimal Therapeutic Dose of Yondelis® in Combination with Doxorubicin in Patients with Untreated Metastatic Soft Tissue Sarcomas and Advanced Pre-Treated Anthracycline," Clinical Cancer Research, Vol. 9, No. 16, pg. 6081S (December 2003). |                |
|                        |                          | Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, page 36, 1975   |                |
|                        |                          | Goodman & Gilman's The Pharmaceutical Basis of Therapeutics (9 <sup>th</sup> edition), page 930, 1996  |                |
|                        |                          | Goodman & Gilman's The Pharmaceutical Basis of Therapeutics (9 <sup>th</sup> edition), pages 1230. 1232, 1996  |                |
|                        |                          | Gore et al., "Phase I Combination Study of Trabectedin and Capecitabine in Patients With Advanced Malignancies," Poster Presentation, 42nd ASCO Annual Meeting held on June 2-6, 2006, Atlanta, Georgia  |                |
|                        |                          | Grever et al., "The National Cancer Institute: Cancer Drug Discovery and Development Program", Seminars in Oncology, vol. 19, no. 6, 622-638, December 1992  |                |
|                        |                          | Grosso et al., "Steroid Premedication Markedly Reduces Liver and Bone Marrow Toxicity of Trabectedin in Advanced Sarcoma," European Journal of Cancer 42:10, 1484-1490 (2006).   |                |

| Substitute for form 1449A/PTO     |                        | Complete if Known |
|-----------------------------------|------------------------|-------------------|
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|                        |                          | Gurtler, J.S. et al., "Trabectedin in third line breast cancer: a multicenter, randomized, phase II study comparing two administration regimens," Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings, vol. 23, no. 16S, part I of II (June 1 Supplement), Abstract No. 625, 2005       |                |
|                        |                          | Hendriks, H.R. et al., "High antitumor activity of ET743 against human tumor xenografts from melanoma, non-small-cell lung and ovarian cancer," Annals of Oncology, vol. 10, pages 1233-1240, 1999   |                |
|                        |                          | Hidalgo, M., et al., "A phase I and pharmacokinetic (PK) study of ET-743, a novel minor groove binder of marine origin administered on a daily x 5 schedule," 23rd European Society for Medical Oncology Congress, Abstract No. 613P, November 6-10, 1998  |                |
|                        |                          | Hillebrand, M.J.X. et al., "Pharmacokinetics of ecteinascidin-743 (ET-743) in three phase I studies," Annals Oncology, Abstract No. 455, 1998  |                |
|                        |                          | Holmes, "Paclitaxel Combination Therapy in the treatment of Metast Breast Cancer: A Review," Seminars in Oncology, vol. 23, pp. 46-56, 1996  |                |
|                        |                          | Hornicek et al., "Effect of Ecteinascidin-743 and Plasminogen related Protein B on a Human Chondrosarcoma Xenograft Tumor in Mice," Clinical Cancer Research, Vol. 7 Supplement P3734S-3734S, Abstract 398 (November 2001)   |                |
|                        |                          | Izbicka, E. et al., "In vitro antitumor activity of the novel marine agent,<br>Ecteinascidin-743 (ET-743, NSC- 648766) against human tumors explanted<br>from patients," Annals of Oncology, vol. 9, pages 981-987, 1998   |                |
|                        |                          | Jimeno, J.M. et al., "Enhancing the preclinical in vivo antitumor activity of ecteinascidin 743, a marine natural product currently in phase II clinical trials," Proceedings of the 1999 AACR-NCI-EORTC International Conference, Clinical Cancer Research, Volume 5, Abstract No. 306, November 1999 |                |
|                        |                          | Jimeno, J. et al., "Phase I and pharmacokinetic (PK) study of Et-743, a novel minor groove binder of marine origin on a daily [times] 5 schedule," 1998 ASCO Annual Meeting Proceedings, Abstract No. 737, 1998  |                |
|                        |                          | Jimeno, Jose et al., "Adding Pharmacogenomics to the Development of New Marine-Derived Anticancer Agents," Journal of Translational Medicine, volume 4, issue 3, January 9, 2006, downloaded from the internet website: << http://www.translational-medicine.com/content/4/1/3>>.                      |                |
|                        |                          | Jin, et al., Ecteinascidin-743, A Transcription-Targeted Chemotherapeutic that Inhibits MDR I Activation. Proc. Natl. Acad. Sci. USA, 97, 6775-9, 2000.  |                |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.L./ (02/27/2008)

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|                        |                          | Proceedings of the AACR, Vol. 42, Abstract 4354 (March 2001).   |    |
|                        |                          | Kanzaki et al., "Microsatellite Instability (MSI) Induced by Ecteinascidin743 and Protection with Aspirin," from the 93rd Annual Meeting of the American Association for Cancer Research, Abstract 5382 (April 6-10, 2002), Vol. 43, March 2002, page 1087.   |    |
|                        |                          | Kovalcik et al., "The Stability of Cyclophosphamide in Lyophilized Cakes. part I. Mannitol, Lactose, and Sodium Biocarbonate as Excipients," Journal of Parenteral Science and Technology, vol. 42, no. 1, Jan-Feb. 1988, pp. 29-37 Laverdiere et al., "Phase II Study of Ecteinascidin 743 In Heavily Pretreated   |    |
|                        |                          | Patients with Recurrent Osteosarcoma", Cancer, American Cancer Society, Philadelphia, PA, August 15, 2003, vol. 98:4, pages 832-840, XP002314512  |    |
|                        |                          | Leonetti et al., "Antitumoral Effect of the G-quadraplex Interactive Compound RHPS4 on Human Melanoma Cells Possessing Relatively Long Telomeres," from the Proceedings of the AACR, Volume 45, March 2004.   |    |
|                        |                          | Lyass et al., "Phase I Study of Doxil-Cisplatin Combination Chemotherapy in Patients with Advanced Malignancies," Clinical Cancer Research, vol. 7, pages 3040-3046, October 2001, XP8086753  |    |
|                        |                          | Maier et al., "In vitro inhibition of endothelial cell growth by the antiangiogenic drug AGM-1470 (TNP-470) and the antiendoglin antibody TEC-11," Anti-Cancer Drugs, vol. 8, pp. 238-244, 1997   |    |
|                        |                          | Magro et al., "The Role of PARP and PARP Inhibitors in Yondelis (Trabectedin) Mediated Cytotoxicity," Abstract and Presentation from the AACR Annual Meeting, April 17, 2007.   |    |
|                        |                          | Manzanares et al., "Advances in the Chemistry and Pharmacology of Ecteinascidins, A Promising New Class of Anticancer Agents," Curr. Med. Chem Anti-Cancer Agents, 2001, vol. 1, pp. 257-276  |    |
|                        |                          | Martinez, et al., Phthalascidin, A Synthetic Antitumor Agent with Potency and Mode of Action Comparable to Eeteinaseidin 743. Proc. Natl. Acad. Sci. USA 96; 3496-501, 1999   |    |
|                        |                          | Martinez, E. J. et al., A New, More Efficient, and Effective Process for the Synthesis of a Key Pentacyclic Intermediate for Production of Ecteinascidin and Phthalascidin Antitumor Agents. Org. Lett. 2, 993-6, 2000.   |    |
|                        |                          | Menchaca et al., "Synthesis of Natural Ecteinascidins (ET-729, ET-745, ET-759B, ET-736, ET-637, ET-594) from Cyanosafracin B," J. Org. Chem., published on web October 21, 2003, pp. 8859-8866  |    |

| Substitute for form 1449A/PTO     |                        | Complete if Known |
|-----------------------------------|------------------------|-------------------|
|                                   | Application Number     | 10/579,160        |
| INFORMATION DISCLOSURE            | Filing Date            | March 1, 2007     |
| STATEMENT BY APPLICANT            | First Named Inventor   | Mary Ellen Rybak  |
|                                   | Art Unit               | 1623              |
| (Use as many sheets as necessary) | Examiner Name          | Lewis, Patrick T. |
| Sheet 8 of 11                     | Attorney Docket Number | 13566.105023      |

|                        |                          | NON PATENT LITERATURE DOCUMENTS   |     |
|------------------------|--------------------------|---|-----|
| Examiner<br>Initials * | Cite<br>No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.  McLeod, "Clinically relevant drug-drug interactions in oncology," Br. J. Clin. | T 2 |
|                        |                          | Pharmacol., 45:539-544 (1998).  McMeekin, D.S. et al., "Final results of a phase II study of weekly trabectedin in second/third line ovarian carcinoma," Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings, Vol. 23, No. 16S, Part I of II (June 1 Supplement), Abstract No. 5011, May 13-17, 2005                             |     |
|                        |                          | Meco et al., "Effective combination of ET-743 and doxorubicin in sarcoma: preclinical studies," Cancer Chemother. Pharmacol. 52: 131-138 (2003).  |     |
|                        |                          | Meco et al., "The combination of ET-743 and Irinotecan is active in preclinical models in rhabomyosarcoma," presented at the 16th EORTC-NCI-AARC Symposium on Molecular Targets and Cancer Therapeutics held in Geneva on September 28 - October 1, 2004.   |     |
|                        |                          | Merck Manual on-line edition version, "Types: Overview of Cancer," 4 pages, downloaded from internet website << <a href="http://www.merck.com/mmhe">http://www.merck.com/mmhe</a> >>, February 2003   |     |
|                        |                          | Michaelson, M.D. et al., "Phase II study of three hour, weekly infusion of trabectedin (ET-743) in men with metastatic, androgen-independent prostate carcinoma (AIPC)," Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings, Vol. 23, No. 16S, Part I of II (June 1 Supplement), Abstract No. 4517, May 13- 17, 2005            |     |
|                        |                          | Minuzzo, M. et al., "Interference of Transcriptional Activation by the Antineoplastic Drug Ecteinascidin.743." Proc. Natl. Acad. Sci. USA 97, 6780-4, 2000  |     |
|                        |                          | Moore et al., "Sequencing evaluation of ET-743 combinations with standard chemotherapy agents against a panel of human tumor cell lines," Clinical Cancer Research, Vol. 6, Abstract 504 (November 2000).   |     |
|                        |                          | Morioka et al., "Antiangiogenesis Treatment Combined with Chemotherapy Produces Chondrosarcoma Necrosis," Clinical Cancer Research, Vol. 9, 1211-1217, March 2003.  |     |
|                        |                          | Pharma Mar Press Release, "PharmaMar Differs with CPMP Opinion", Pharma Mar Grupo Zeltia, < <a href="http://www.pharmamar.com/en/press/news_release.cfm">http://www.pharmamar.com/en/press/news_release.cfm</a> >, July 24, 2003  |     |
|                        |                          | Pharma Mar Press Release, "PharmaMar Receives EMEA Appeal Decision on Yondelis in Soft Tissue Sarcoma", Pharma Mar Grupo Zeltia, < <a href="http://www.pharmamar.com/en/press/news_release.cfm">http://www.pharmamar.com/en/press/news_release.cfm</a> >, November 20, 2003   |     |
|                        |                          | Pharma Mar Press Release, "YONDELIS(r) STS-201 Efficacy and Safety Data Presented at ASCO 2007" Pharma Mar Grupo Zeltia, << http://www.pharmamar.com/en/press>>, June 5, 2007   |     |

| Substitute | for form 1449A/PTC | )      |            |                        | Complete if Known |
|------------|--------------------|--------|------------|------------------------|-------------------|
|            |                    |        |            | Application Number     | 10/579,160        |
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| STAT       | EMENT B            | ΥΑΙ    | PPLICANT   | First Named Inventor   | Mary Ellen Rybak  |
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| Sheet      | 9                  | of     | 11         | Attorney Docket Number | 13566.105023      |

|                        |              | NON PATENT LITERATURE DOCUMENTS   | _  |
|------------------------|--------------|---|----|
| Examiner<br>Initials * | Cite<br>No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.                         | T² |
|                        |              | Pharma Mar Press Release, "The European Commission Authorizes YONDELIS(r) Commericalization for Soft Tissue Sarcoma" Pharma Mar Grupo Zeltia, << http://www.pharmamar.com/en/press>>, September 20, 2007  |    |
|                        |              | Pommier, et al., "DNA Sequence- And Structure-Selective Alkylation of Guanine N2 in the DNA Minor Groove by Ecteinascidin 743, a Potent Antitut:I1or Compound from the Caribbean Tunicate Ecteinascidia Turbinata." Biochemistry 35, 13303-9, 1996                                      |    |
|                        |              | Rinehart, K.L., "Antitumor Compounds from Tunicates." Moo. Res. Rev. 20, 1-27, 2000   |    |
|                        |              | Riccardi et al., "Preclinical Activity and Biodistribution of Ecteinascidin 743 (ET-743) and Doxorubicin (DOX) Combinations in Human Rhabdomyosarcoma," from the AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics of October 29 – November 2, 2001, Abstract 405. |    |
|                        |              | Riccardi et al., "Effective Combinations of ET-743 and Doxorubicin for Tumor Growth Inhibitions Against Murine and Human Sarcomas in Athymic Mice," from the Proceedings of the AACR, Vol. 42, Abstract 1132 (March 2001).  |    |
|                        |              | Riccardi et al., "Combination of trabectedin and irinotecan is highly effective in a human rhabdomyosarcoma xenograft," Anti-Cancer Drugs, 16:811-815 (2005).   |    |
|                        |              | Riofrio, M. et al., "Ecteinascidin-743 (ET-743) 24 hours continuous infusion (CI): Clinical and pharmacokinetic phase I study progressive report," 23rd European Society for Medical Oncology Congress, Abstract 639P, November 6-10, 1998  |    |
|                        |              | Robert et al.,"Pharmacokinetics of Doxorubicin in Sarcoma Patients," Eur. J. Clin. Pharmocol., vol. 31, pp. 695-699, 1987   |    |
|                        |              | Ryan, DP et al., "Phase I and Pharmacokinetic Study of Ecteinascidin-743<br>Administered as a 72 hours Continuous Intravenous Infusion in Patients with<br>Solid Malignancies", Clinical Cancer Research, Vol. 7, pp. 231-242, 2001   |    |
|                        |              | Saito et al., "Synthesis of Saframycins- 3," J. Org. Chem., 54, 5391, 1989  |    |
|                        |              | Sakai et al., "Additional Antitumor Ecteinascidins from a Caribbean Tunicate: Crystal Structures and Activities in vivo," Proc. Natl. Acad. Sci., vol. 89, Dec. 1992, pp. 11456-11460   |    |
|                        |              | Sato et al., "Multicenter Phase II Trial of Weekly Paclitazel for Advanced or Metastatic Breast Cancer: the Saitama Breast Cancer Clincal Study Group (SBCCSG-01)," Japanese Journal of Clinical Oncology, Vo. 33, no. 8, pp. 371-376, August 2003                                      |    |
|                        |              | Scotlandi et al., "Effectiveness of Ecteinascidin-743 against Drug-sensitive and –resistant Bone Tumor Cells," Clinical Cancer Research, 8:3893-3903 (December 2002)  |    |

| Substitute | for form 1449A/PTC | )      |            |                        | Complete if Known |
|------------|--------------------|--------|------------|------------------------|-------------------|
|            |                    |        |            | Application Number     | 10/579,160        |
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|------------------------|--------------|--|-----|
| Examiner<br>Initials * | Cite<br>No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.                                      | T 2 |
|                        |              | Sessa et al., "Trabectedin for Women with Ovarian Carcinoma After Treatment with Platinum and Taxane Fails," Journal of Clinical Oncology," vol. 23,no. 9, pp. 1867-1874, March 20, 2005   |     |
|                        |              | Smyth, "Rationale for Drug Combinations," European Journal of Cancer, 39, 1816-1817 (2003).  |     |
|                        |              | Taamma et al., "Phase I Clinical Study of ecteinascidin-743 (ET-743)," Eur. J. Cancer, 33 Suppl. 8, S247-S248, 1997, Abstract  |     |
|                        |              | Taamma, A. et al., "Ecteinascidin-743 (ET-743) 24 hours continuous infusion (CI): clinical and pharmacokinetic phase I study in solid tumor patients (PTS). Preliminary Results" 1998 ASCO Annual Meeting Proceedings, Abstract No. 890, 1998  |     |
|                        |              | Taamma, A. et al., "Phase I clinical study of ecteinascidin-743 (ET-743) as a 24 hours continuous intravenous infusion (CI) in patients (pts) with solid tumors (st): A progress report," ECCO, vol. 9, Abstract No. 1119, September 18, 1997  |     |
|                        |              | Taamma et al., "Phase I and Pharmcokinetic Study of Ecteinascidin-743, a New Marine Compound, Adminstered as a 24 hours Continuous Infusion in Patients with Solid Tumors", J. of Clinical Oncology, vol. 19, no. 5, pp. 1256-1265, 2001   |     |
|                        |              | Tabor et al., "Anti oxidation Potential of Indole Compounds-Structure Activity Studies," Biological Reactive Intermediates IV, p. 833-836, 1990  |     |
|                        |              | Takebayashi et al., "Poisoning of Human DNA Topoisomerase I by Ecteinascidin 743, An Anticancer Drug That Selectively Alkylates DNA in the Minor Groove." Proc. Natl. Acad. Sci. USA 96, 7196-201 1999   |     |
|                        |              | Takahashi et al., "Ecteinascidin 743 (ET-743) and doxorubicin produce synergistic cytotoxic effects in soft tissue sarcoma lines HT-1080 and HS-18," Clinical Cancer Research, Vol. 6, Abstract 208 (November 2000).   |     |
|                        |              | Takahashi et al., "Sequence-dependent Enhancement of Cytotoxicity Produced by Ecteinascidin 743 (ET-743) with Doxorubicin or Paclitaxel in Soft Tissue Sarcoma Cells," Clinical Cancer Research, 7: 3251-3257 (October 2001).  |     |
|                        |              | Ten Hagen et al., "Pegylated Liposomal Tumor Necrosis Factor-Alpha Results in Reduced Toxicity and Synergistic Antitumor Activity after Systemic Administration in Combination with Liposomal Doxorubicin (Doxil) in soft tissue Sarcoma-Bearing Rats," Int. J. Cancer, vol. 97, pages 115-120, 2002 |     |
|                        |              | Twelves et al., "A Phase I and Pharmacokinetic (PK) study of Et-743 evaluating a 3 hours (h) intravenous (iv) infusion (I) in patients (pts) with solid tumors," Clinical Cancer Research, Abstract #307, 5 (11, suppl. 3790S-3791S) 1999  |     |

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| Substitute | e for form 1449A/PTO |        |            |                        | Complete if Known |
|------------|----------------------|--------|------------|------------------------|-------------------|
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|                        |              | Twelves, C.J. et al., "Phase I clinical and pharmacokinetic (PK) study of ecteinascidin-743 (ET-743) given as a one hour infusion every 21 days," 1998 ASCO Annual Meeting Proceedings, Abstract No. 889, 1998  |     |
|                        |              | Twelves, C.J. et al., "Phase I and pharmacokinetic study of ecteinascidin-743 (ET-743) given as a one hour infusion every 21 days," ECCO, vol. 9, Abstract No. 1107, September 18, 1997   |     |
|                        |              | Valoti, "Ecteinascidin-743, a New Marine Natural Product with Potent Antitumor Activity on Human Ovarian Carcinoma Xenografts," Clin. Cancer Res., vol. 4, pages 1977-83, August 1998   |     |
|                        |              | Valoti, G., et al., "Ecteinascidin-743 (ET-743), a marine natural compound, shows antitumor activity against human ovarian carcinoma xenografts," Novel Therapeutics and Pharmacology, pageS39, Abstract PP179, 1998  |     |
|                        |              | van Kesteren et al. "Clinical Pharmacology of the Novel Marine-derived<br>Anticancer Agent Ecteinascidin 743 Administered as a 1- and 3-h Infusion in a<br>Phase I Study," Anti-Cancer Drugs, Vol. 13, No.4, pgs. 381-393, April 2002                           |     |
|                        |              | van Kesteren et al. "Yondelis® (trabectedin, ET-743): The Development of an Anticancer Agent of Marine Origin" Anti-Cancer Drugs, Vol. 14, No.7, pgs. 487-502, August 2003  |     |
|                        |              | Villalona-Calero, M. et al., "A phase I and pharmacokinetic study of ET-743, a novel DNA minor groove binder of marine origin, administered as a 1-hour infusion daily x 5 days," Annals Oncology, Abstract 453, 1998   |     |
|                        |              | Villalona-Calero, M. et al., "Final results of a Phase I and pharmacokinetic (PK) study of the marine minor groove binder ET-743 on a daily x 5 schedule," 1999 ASCO Annual Meeting Proceedings, Abstract No. 691, 1999   |     |
|                        |              | Wiesenthal, "Is one 'sensitive' drug better than another?" downloaded from internet website << http://weisenthal.org/feedback.html>>, Feb. 4, 2002  |     |
|                        |              | Wright et al., "Antitumor Tetrahydroisoquinonline Alkaloids from the Colonial Ascidian Ecteinascidia Turbinata", J. Org. Chem., vol. 55, pp. 4508-4512, 1990  |     |
|                        |              | Zewail-Foote, et al., "Ecteinascidin 743: A Minor Groove Alkylator that Bends DNA Toward the Major Groove," J. Med. Chem. 42, 2493-7, July 15, 1999   |     |

|  | Examiner<br>Signature | /Patrick Lewis/ (02/27/2008) | Date<br>Considered |  |
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